

wherein -LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula, -(CH₂)_bC(O)- where b is an integer from 1-5, a diester diradical of the formula, -C(O)-(CH₂)_c-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula -C(O)-O-(CH₂)_d-O-C(O)- where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-(CH₂)_c-C(O)-, or -R-C(O)-O-(CH₂)_c-O-C(O)- where c is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone and p-dioxanone;

wherein -G is a leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, [or] and tresyl;

wherein a combination of the first and second mixtures is initially liquid and then cures on the surface of tissue to give a flexible, substantive matrix which bonds to the tissue and has a burst strength greater than about 10 mmHg.

171,1731
2. (Amended) The adhesive [mixture] composition of claim 1 wherein the protein in the first mixture is about 35-45 wt/vol % serum albumin.

171,1731
9. (Amended) An in vivo method of adhering tissue comprising the steps of topically applying and bonding an adhesive [mixture] composition of claim 1 to the tissue.

171,1731
10. (Amended) An in vivo method of sealing air leaks in pulmonary tissues comprising the step of topically applying and curing the adhesive [mixture] composition of [claims] claim 1 to an air leak site in the pulmonary tissue.

171,1731
* 11. (Amended) An in vivo method to prevent post-surgical adhesions comprising the step of topically applying and

17/173 I curing the adhesive [mixture] composition of [claims] claim 1 to tissue surrounding a surgical site.

12. (Amended) An in vivo method to seal tissue comprising the step of topically applying and bonding the adhesive [mixture] composition of [claims] claim 1 to tissue to prevent or control blood or other fluid leaks.

15. (Amended) The adhesive [mixture] composition of claim 1 wherein -LM- is a diester diradical of the formula -C(O)-
(CH₂)_c-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated.

16. (Amended) The adhesive composition of claim [15] wherein -LM- is [a] an oligomeric diradical derived from polyglycolic acid.

17. (Amended) A method of making a tissue adhesive consisting of the step of forming a mixture of
i) a first aqueous mixture of about 20-60 wt/vol % serum albumin in about 0.01-0.25 molar buffer at a pH in a range of about 8.0-11.0,
ii) a second aqueous mixture of about 50-800 mg/ml of a crosslinking agent having a molecular weight in a range of about 1,000-15,000, wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein -PEG- is a diradical fragment represented by the formula

-O-(CH₂-CH₂-O-)_a-

wherein a is an integer from 20-300;

wherein -LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula[,] -(CH₂)_bC(O)- where b is an integer from 1-5, a diester diradical of the formula[,] -C(O)-

cont 3

$(\text{CH}_2)_c-\text{C}(\text{O})-$ where c is an integer from 2-10 and where the aliphatic portion of the radical may be saturated or unsaturated, a dicarbonate diradical of the formula $-\text{C}(\text{O})-\text{O}- (\text{CH}_2)_d-\text{O}-\text{C}(\text{O})-$ where d is an integer from 2-10, and an oligomeric diradical represented by the formulas $-\text{R}-\text{C}(\text{O})-$, $-\text{R}-\text{C}(\text{O})-(\text{CH}_2)_c-\text{C}(\text{O})-$, or $-\text{R}-\text{C}(\text{O})-\text{O}- (\text{CH}_2)_d-\text{O}-\text{C}(\text{O})-$ where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone and p-dioxanone; and

wherein $-\text{G}$ is a leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, [or] and tresyl; and

wherein a combination of the first and second mixtures is initially liquid and then cures on the surface of tissue to give a flexible, substantive matrix which bonds to the tissue and has a burst strength greater than about 10 mmHg.

MSQH 1
a 1

37. The method of claim 36 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

$-\text{O}-(\text{CH}_2-\text{CH}_2-\text{O}-)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula $-\text{C}(\text{O})-$, a monoester diradical of the formula $-(\text{CH}_2)_b\text{C}(\text{O})-$ where b is an integer from 1-5, a diester radical of the formula $-\text{C}(\text{O})-(\text{CH}_2)_c-\text{C}(\text{O})-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula $-\text{C}(\text{O})-\text{O}- (\text{CH}_2)_d-\text{O}-\text{C}(\text{O})-$ where d is an integer from 2-10, and an oligomeric diradical represented by the formulas $-\text{R}-\text{C}(\text{O})-$, $-\text{R}-\text{C}(\text{O})-(\text{CH}_2)_c-\text{C}(\text{O})-$, or $-\text{R}-\text{C}(\text{O})-\text{O}- (\text{CH}_2)_d-\text{O}-\text{C}(\text{O})-$ where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone and p-dioxanone; and

a4
integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

a4
-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

a5
40. The method of claim 17 wherein the second mixture is about 50-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

a6
51. The method of claim 50 wherein the air leak is in a pulmonary system.

CHS95
71. The method of claim 70 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

a7
-PEG- is a diradical fragment represented by the formula

$-\text{O}-\text{(CH}_2-\text{CH}_2-\text{O}-)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula $-\text{C}(\text{O})-$, a monoester diradical of the formula $-\text{(CH}_2)_b\text{C}(\text{O})-$ where b is an integer from 1-5, a diester radical of the formula $-\text{C}(\text{O})-\text{(CH}_2)_c-\text{C}(\text{O})-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula $-\text{C}(\text{O})-\text{O}-\text{(CH}_2)_d-\text{O-C}(\text{O})-$ where d is an integer from 2-10, and an oligomeric diradical represented by the formulas $-\text{R-C}(\text{O})-$, $-\text{R-C}(\text{O})-\text{(CH}_2)_c-\text{C}(\text{O})-$, or $-\text{R-C}(\text{O})-\text{O}-\text{(CH}_2)_d-\text{O-C}(\text{O})-$ where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of

a7
lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

a8
74. The method of claim 71 wherein the second mixture is about 50-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

ChSOU
103. The method of claim 102 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

-O-(CH₂-CH₂-O-)_a-

where a is an integer from 20-300;

a9
-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -(CH₂)_bC(O)- where b is an integer from 1-5, a diester radical of the formula -C(O)-(CH₂)_c-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula -C(O)-O-(CH₂)_d-O-C(O)- where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-(CH₂)_c-C(O)-, or -R-C(O)-O-(CH₂)_d-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

a/10
106. The method of claim 103 wherein the second mixture is about 50-300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000-5,000.

a/11
130. The method of claim 129 wherein the matrix has a burst pressure of about 34 mmHg or greater.

a/11
131. The method of claim 130 wherein the matrix has a burst pressure of about 90 mmHg or greater.

a/12
132. The method of claim 131 wherein the matrix has a burst pressure of about 130 mmHg or greater.

Chris P1
138. The method of claim 137 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

-O- (CH₂-CH₂-O-)_a-

where a is an integer from 20-300;

a/12
-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -(CH₂)_bC(O)- where b is an integer from 1-5, a diester radical of the formula -C(O)-(CH₂)_c-C(O)-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula -C(O)-O-(CH₂)_d-O-C(O)- where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-(CH₂)_c-C(O)-, or -R-C(O)-O-(CH₂)_d-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and